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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/803,187	03/18/2004	Thomas Christoph	029310.53299US	5120

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EXAMINER	
KUDLA, JOSEPH S	
ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/803,187	CHRISTOPH, THOMAS	
	Examiner	Art Unit	
	JOSEPH S. KUDLA	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-41 and 44-73* is/are pending in the application.

4a) Of the above claim(s) *38,40,41,44-47,52,53 and 58-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,39,48-51,54-57 and 71-73* is/are rejected.

7)☐ Claim(s) *39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Foreword

1. Applicants' Amendment-After Final Rejection, amended specification, submittal of an English language translation of DE 101 46 275.1 and amended claim set, filed March 21, 2008, are acknowledged. Applicants' amendments to instant claims 37, 46, 48 and 61 are acknowledged. With respect to Applicants' Arguments/Remarks in the correspondence, the arguments and request for reconsideration have been fully considered and are found to be persuasive due to the submission of the translation of DE 101 46 275.1. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejection and objection are newly applied. They constitute the complete set presently applied to the instant specification. This action is **NON-FINAL**.

Claims 37, 39, 48-51, 54-57 and 71-73 are presented for examination on the merits as they read upon the elected subject matter.

Priority

2. This application claims the benefits as a continuation of PCT Application No. PCT/EP02/10460, filed on September 18, 2002, and Foreign Priority Application DE 101 46 275.1, filed September 18, 2001. Priority is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear to the Examiner whether both compounds from group (i) and (ii) have to be in the form of a pure enantiomer or pure diastereoisomer or whether only those compounds of group (ii).

Appropriate correction is required.

Claim Rejections - 35 USC § 103

(New grounds of rejection precipitated by Applicants' amendment)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 37, 48-51, 54, 57 and 71-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Chutka et al. ("Urinary Incontinence in the Elderly: Drug Treatment Options," 1998, Drugs, Volume 56, Number 4, Pages 587-595** and cited by Applicant), in view of **Buschmann (US Patent 5,811,582)** and **Andersson et al ("The pharmacological treatment of urinary incontinence," 1999, British Journal of Urology International, 84:923-947** and cited by Applicant).

The instant invention claims a composition of an analgesic and an anti-muscarinic agent. The composition can be put into a pharmaceutical composition using pharmaceutically suitable additives or auxiliary substances .

Chutka et al. teach drugs such as anticholinergics and opioids have the ability to impair detrusor contraction (page 593, column 2, under Medications and Table 1).

Chutka et al does not teach the motivation to form a composition of (+)(2R, 3R)-1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol with an anti-muscarinic agent (e.g., oxybutinin) or the composition as a pharmaceutical formulation.

Buschmann et al. teach "There is currently a world-wide need for additional pain therapy which is not exclusively opioid but which exhibits good efficacy" (column 1, lines 10-12). Buschmann et al. teach the object of the invention is to develop substances having an analgesic effect without "the side effects which are typical of opioids" (column 1, lines 46-50). Buschmann et al. teach the compound (2R, 3R)-1-dimethylamino-3-(3-

methylphenyl)-2-methylpentan-3-ol has a greater analgesic effect than tramadol (column 1, lines 58-59, column 5, lines 64-65, column15, Table). Buschmann et al. teach the compounds can be formulated into a drug product with the use of fillers, solvents *inter alia* (column 5, lines 18-26).

Andersson et al. disclose pharmaceutical substances that are known to treat urinary incontinence (Title) and include anti-muscarinic (*i.e.*, anticholerinergic) agents such as atropine, propantheline, emepronium, trospium, tolterodine, darifenacin, oxybutynin and propiverine (page 924 and 925, Table 2). Andersson et al. teach that one such anti-muscarinic agent oxybutinin has well documented efficacy in the treatment of detrusor hyperactivity and has been not only formulated into tablets but an extended-release product called OROS® (page 930, column 2, third and fifth full paragraphs).

It would have been obvious to one of ordinary skill in the art at the time of the invention that because Chutka et al. teach anticholinergics and opioids have the ability to impair detrusor contraction, one of ordinary skill in the art would be motivated to combine the two therapies for the treatment of urinary incontinence or overactive bladder and have a reasonable expectation of success of treating the conditions based on the literature by Chutka et al. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art."

In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted).

It would have been obvious to one of ordinary skill in the art at the time of the invention that the compound (2R, 3R)-1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol has at least some opioid receptor activity due to the teachings of Buschmann et al. (*i.e.*, the column 1, lines 10-12 and line 50 citations) and because of the comparison of the compound to tramadol (i.e., a well known fully synthetic opioid). Furthermore, it would have been obvious to one of ordinary skill in the art at the time of the invention that the compound (2R, 3R)-1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol would exist as a racemic mixture of (+) and (-) enantiomeric forms.

In conclusion, it would have been obvious to one of ordinary skill in the art at the time of the invention that the compound (2R, 3R)-1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol would contain the (+) enantiomer and act as an opioid ***and*** when combined with an anti-muscarinic (*e.g.*, oxybutinin) would have the ability to treat urinary incontinence or overactive bladder thus providing the motivation to combine the two compounds to make the composition of instant claim 37 and rendering instant claim 37 obvious.

It would have been obvious to one of ordinary skill in the art at the time of the invention that because the compound (2R, 3R)-1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol is represented by the generic formula I in instant claim 37, wherein the compound is formed with the substituents being X=OH, R1=C2H5, R2=H, R3=CH3, R9, R11, R12 and R13=H and R10=OCH3, coupled with the fact that all of these

options are available within instant claims 48-51 and 54 will render these claims obvious. It would have been obvious to one of ordinary skill in the art that the compound (2R, 3R)-1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol would exist as a racemic mixture of (+) and (-) enantiomeric forms and contain the (+) enantiomer, thus rendering instant claim 57 obvious. It would have been obvious to one of ordinary skill in the art at the time of the invention that because Andersson et al. disclose pharmaceutical substances that are known to treat urinary incontinence and include anti-muscarinic agents such as tolterodine, darifenacin and oxybutynin, instant claims 71 and 72 are rendered obvious. It would have been obvious to one of ordinary skill in the art at the time of the invention that because Andersson et al. and Buschmann et al. teach a pharmaceutical formulations for oxybutinin and excipients for (2R, 3R)-1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol , instant claim 73 is rendered obvious.

5. Claims 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Chutka et al. ("Urinary Incontinence in the Elderly: Drug Treatment Options," 1998, Drugs, Volume 56, Number 4, Pages 587-595** and cited by Applicant), in view of **Buschmann (US Patent 5,811,582), Andersson et al ("The pharmacological treatment of urinary incontinence," 1999, British Journal of Urology International, 84:923-947** and cited by Applicant) and **Buschmann et al. (US Patent 6,248,737 and hereinafter '737)**.

The instant invention claims a composition of an analgesic and an anti-muscarinic agent. The composition can be put into a pharmaceutical composition using pharmaceutically suitable additives or auxiliary substances .

Chutka et al. teach drugs such as anticholinergics and opioids have the ability to impair detrusor contraction (page 593, column 2, under Medications and Table 1).

Buschmann et al. teach "There is currently a world-wide need for additional pain therapy which is not exclusively opioid but which exhibits good efficacy" (column 1, lines 10-12). Buschmann et al. teach the object of the invention is to develop substances having an analgesic effect without "the side effects which are typical of opioids" (column 1, lines 46-50). Buschmann et al. teach the compound (2R, 3R)-1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol has a greater analgesic effect than tramadol (column 1, lines 58-59, column 5, lines 64-65, column15, Table). Buschmann et al. teach the compounds can be formulated into a drug product with the use of fillers, solvents *inter alia* (column 5, lines 18-26).

Andersson et al. disclose pharmaceutical substances that are known to treat urinary incontinence (Title) and include anti-muscarinic (*i.e.*, anticholerinergic) agents such as atropine, propantheline, emepronium, trospium, tolterodine, darifenacin, oxybutynin and propiverine (page 924 and 925, table 2 and). Andersson et al. teach that one such anti-muscarinic agent oxybutinin has well documented efficacy in the treatment of detrusor hyperactivity and has been not only formulated into tablets but an extended-release product called OROS® (page 930, column 2, third and fifth full paragraphs).

Please refer at 4 *supra* for the rejection of instant claims 37, 48-51, 54, 57 and 71-73.

Chutka et al does not teach enantiomerically pure (+)-(2R, 3R)-1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol is useful in the composition.

'737 teaches a method of making and separating the (+) enantiomer of (2R, 3R)-1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol (Example 1, column 6, line23 to column 7, line 61). '737 teaches that the (+) enantiomer of (2R, 3R)-1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol is a superior analgesic compared to the racemic mixture or (-) enantiomer (column 23, Table).

It would have been obvious to one of ordinary skill in the art at the time of the invention that, although it was shown (2R, 3R)-1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol was a superior analgesic having opioid activity compared to tramadol as taught by Buschmann et al., '737 has shown the enantiomerically pure (+)-(2R, 3R)-1-dimethylamino-3-(3-methylphenyl)-2-methylpentan-3-ol to be much more effective as an analgesic than the racemic mixture or the (-) enantiomer. One of ordinary skill in the art would have been motivated to utilize that most effective compound to have the greatest expectation of success when used in combination with an antimuscarinic agent to treat urinary incontinence or overactive bladder, thus rendering instant claims 54 and 55 obvious.

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JOSEPH S. KUDLA whose telephone number is (571)270-3288. The examiner can normally be reached on 9am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Joseph S. Kudla/
Examiner, Art Unit 1611
September 4, 2008

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615